REMARKS

Status of the Claims

Claims 1-4 are currently pending in the application. Claims 1-4 stand rejected. The Examiner objects to claim 1. Claim 1 has been amended without prejudice or disclaimer. No new matter has been added by way of the present amendments. Specifically, the amendment to claim 1 is supported by the specification at, for instance, page 6, lines 17-24 and page 8, lines 20-25. Reconsideration is respectfully requested.

Amendments to the Specification

Paragraphs [0033], [0034] and [0038] of the published application have been amended herein to correct typographical errors and errors as to scientific clarity, as explained in more detail in the English language translation of the Amendment to the Written Description under PCT Rule 32, submitted to the Japanese Patent Office on May 25, 2004, copies of which were filed in the present application on January 10, 2006.

The amendments to the specification do not in any way introduce new matter into the specification.

The amendments to the specification are supported as follows: paragraphs [0033] and [0034] – amendments are to remove subject matter, the amendment does not add subject matter; paragraph [0038] merely adds a parenthetical phrase which further clarifies the substance contained in the precipitate and is supported elsewhere in the specification at, for instance, page

8, lines 13-16 and lines 20-22, both sections disclosing that the obtained tissue has both chondrocytes and perichondrium cells.

Objections to the Claims

The Examiner objects to claim 1. (*See*, Office Action of November 5, 2007, at page 2, hereinafter, "Office Action"). The Examiner states that the preamble of claim 1 recites "human chondrocytes" whereas step 1 of claim 1 only recites "chondrocytes." Although Applicant believes claim 1 is fully descriptive of the claimed subject matter, to expedite prosecution, claim 1 has been amended without prejudice or disclaimer to recite the term "human" in step 1 of claim 1.

Reconsideration and withdrawal of the objection to claim 1 are respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

Klein-Nulend et al., *Tissue Engineering*, 4(3):305-313, 1998

Claims 1 and 2 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Klein-Nulend et al., *Tissue Engineering*, 4(3):305-313, 1998 (hereinafter referred to as "Klein-Nulend et al."). (*See*, Office Action, at pages 3-4). Applicant traverses the rejection as set forth herein.

The Examiner argues that Klein-Nulend at al. disclose that human auricular perichondrium contains chondrocytes. (*Id.*, at page 2, lines 9 to 8 from the bottom). The Examiner further states that the perichondrium from ear or rib is disclosed as a convenient source of cells with chondrogenic potential, *i.e.* chondrocytes. (*Id.*, at lines 4 to 2). However, Applicant

believes that the Examiner's understanding and interpretation of the disclosure of Klein-Nulend at al. are incorrect.

Histology of cartilage clearly shows that cartilage is composed of a peripheral thin layer of perichondrium and a thick and bulky part including chondrocytes and that perichondrium exists in the cartilage apart from chondrocytes or independent of chondrocytes. (*See*, L.P. Gartner et al., *Color Textbook of Histology*, page 131-134, *inter alia*, page 132, Fig. 7-1, copy of which is attached hereto as Exhibit A). According to the histology of cartilage, perichondrium does not contain chondrocytes themselves, but contain "progenitor cells with chondrogenic potential" which are referred to as "chondrogenic cells." (*See*, Kleein-Nulend et al., at page 305, ABSTRACT, lines 4 to 5, and see, Exhibit A, at page 132, right column, second paragraph, lines 5 to 9).

Thus, "progenitor cells with chondrogenic potential" are distinguishable from "chondrocytes." Klein-Nulend et al. only disclose differentiation of progenitor cells to chondrocytes and do not disclose the method of culturing chondrocytes or co-culturing chondrocytes together with perichondrium. Therefore, Klein-Nulend at al. do not disclose all limitations of the presently claimed invention.

Dependent claim 2 is not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 1.

Reconsideration and withdrawal of the anticipation rejection of claims 1 and 2 are respectfully requested.

Van Osch et al., *Plastics and Reconstructive Surgery*, 2001

Claims 1-4 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Van Osch et al., *Plastics and Reconstructive Surgery*, 2001 (hereinafter referred to as "Van Osch I"). (*See*, Office Action, at pages 4-5). Applicant traverses the rejection as set forth herein.

The Examiner argues that human auricular cartilage is known to be coated with perichondrium. Thus, the Examiner concludes that the chondrocytes isolated by the described method must essentially be coated with the perichondrium and therefore co-cultured together with the perichondrium of the cartilage from which it was isolated. (*Id.*, at page 4, lines 4 to 1 from the bottom). However, Applicant believes that the Examiner's interpretation of the disclosure of Van Osch I is not correct, as described in further detail, below.

Van Osch I, at page 434, left column, "MATERIALS AND METHODS, Origin of Cartilage," discloses that "[c]artilage from the external ear was dissected after carefully removing the perichondrium." This description means that perichondrium was removed by manipulation. Therefore, the chondrocytes isolated by the described method of Van Osch I cannot be coated with the perichondrium.

In the method of Van Osch I, even if chondrocytes were contaminated with perichondrium, perichondrium can be eliminated by a combination of enzymatic treatment and filtration from chondrocytes to be cultured by the following method. A sampled cartilage is sliced and incubated with pronase E, then with collagenase B (type II collagenase), the resulting medium is filtered with a 100 μm filter to isolate the chondrocytes. (*See*, page 434, left column, line 4 from the bottom to right column, line 7, of Van Osch I). Thus, pronase E

roughly breaks up the sampled cartilage, then collagenase B decomposes the produced chondrocyte blocks, which contain collagen E (type II collagen, *see*, Exhibit A, at page 131, right column, lines 1 and 4), into fine chondrocyte cells with a diameter of 10 μm to 30 μm. (*Id.*, at page 133, right column, line 3 from the bottom).

However, perichondrium is not broken up by collagenase B because perichondrium does not contain collagen B (type II collagen). Perichondrium contains type I collagen. (*Id.*, at page 132, right column, second paragraph, lines 5 to 7). Then, filtration with a 100 μm filter enables removal of undigested parts, such as perichondrium, even if they are present in the chondrocyte preparation, and isolatation of chondrocytes to be cultivated, having a diameter of 10 μm to 30 μm.

In light of the facts provided in the above paragraphs, it is clear that Van Osch I cannot anticipate the presently claimed subject matter.

Dependent claims 2-4 are not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 1.

Reconsideration and withdrawal of the anticipation rejection of claims 1-4 are respectfully requested.

Larson et al., *Matrix Biol.*, 2002

Claim 1 stands additionally rejected under 35 U.S.C. § 102(b) as being anticipated by Larson et al., *Matrix Biol.*, 2002 (hereinafter, "Larson et al."). (*See*, Office Action, at pages 5-6). Applicant traverses the rejection as set forth herein.

The Examiner asserts that "Larson et al. teach producing human chondrocytes by co-culturing chondrocytes with their pericellular matrix attached and no exogenous feeder cells were added to the culture." However, the Examiner's assertion is based on an incorrect scientific assumption or reasoning, as explained in further detail, below. Thus, Larson et al. cannot anticipate the presently claimed invention.

Regarding pericellular matrix, Larson et al. disclose the use of "chondrocytes with their *in vivo* formed pericellular matrix." Pericellular matrix is a matrix surrounding chondrocytes. On the other hand, perichondrium exists in a cartilage which is separate from chondrocytes or chondrocytes with pericellular matrix. (*See*, Exhibit A, at page 132, Fig. 7-1). Therefore, perichondrium is distinguishable from pericellular matrix. Based on this distinction, hereinabove explained in detail, Larson et al. cannot anticipate the claimed subject matter.

Larson et al. disclose a culture of chondrocytes in articular cartilage obtained from a human knee. (*See*, Larson et al., at page 350, right column, "2.1 Cell culture"). Although articular cartilage has pericellular matrix (*see*, *Id.*, at page 349, Abstract), articular cartilage has no Perichondrium. This is clearly shown by the description of Exhibit A, page 132, right column, lines 18 to 17 from the bottom, as follows: "Articular cartilage lacks a perichondrium." Further, please review Exhibit A at page 131, right column, lines 14 to 16 and page 133, TABLE 7-1, first row delineating the Type "Hyaline," under the column "Perichondrium" wherein it states, "Perichondrium present in most places (exceptions: articular cartilages and epiphyses)," (*emphases added*).

Therefore, in light of the above disclosure on Exhibit A, it is clearly established on the

record that articular cartilage lacks a perichondrium. Thus, it logically follows that chondrocytes isolated from articular cartilage, such as a knee cartilage, necessarily cannot contain a perichondrium. Finally, it is logical to conclude based on these facts that Larson et al. cannot anticipate the claimed subject matter.

The Examiner also directs Applicant's attention to the supporting disclosure of Long et al., *Development*, Vol. 125, pp. 1067-1073, 1998 (hereinafter, "Long et al."). Long et al. disclose in Fig. l(B) and Fig. 1(C), tibiotarsi obtained from day 12 chicken embryos are covered with perichondrium, and describe that "the perichondrium over the articular surface, which is tightly adherent to the cartilage, remained intact after the manipulation." (*See*, Long et al., at page 1068, left column, "Materials and Methods, Organ culture," and at page 1068, right column, "Gross morphology of perichondrium-free cultures," lines 5 to 7). Thus, Long et al. disclose that "tibiotarsi obtained from Day 12 chicken embryo" have perichondrium on the articular cartilage.

However, it has long been known to one of skill in the art that the articular cartilage of a chicken knee joint, such as "tibiotarsi," is physiologically and anatomically different from human articular cartilage. For example, please consider the proof of this fact disclosed in Graf et al., *International Orthopaedics*, 17:113-119, 1993 (copy of which is attached hereto for the Examiner's convenience as Exhibit B), particularly at page 113, left column, "Summary," which discloses the following (*next page*):

> The articular cartilage and synovial membrane of immature and mature chicken knee joint were studied . . . . The findings differed from human articular cartilage and we concluded that the chicken knee joint is not suitable as a model for human joint degeneration.

Graf et al. further disclose the following at page 117, left column, lines 3 to 1 from the bottom: "Our study shows that that structure of the cartilage of the chicken knee joint differs in a number of ways from the corresponding cartilage in mammals."

Additionally, Graf et al. provide the following statement at page 118, right column, lines 5 to 7: "We think therefore that it is not correct to use chicken for research into experimental ostenarthritis because of these differences."

Considering these descriptions mentioned above, Graf et al. do not necessarily suggest that human articular cartilage has a perichondrium.

Based on the description in the priority documents paragraphs [0017], the Examiner points out that Applicant teaches articular cartilage to have perichondrium. But claim 1 defines cartilage as "a cartilage having said perichondrium." Therefore, in light of the definition of claim 1 and the common knowledge of one of skill in the art, mentioned above, it is clear that the description of articular cartilage in the priority documents is an error and the description should be understood to be deleted from the documents. Actually this error was amended in the process of the PCT preliminary examination by the filing of a written amendment under PCT Rule § 34 with the receiving office, *i.e.*, the Japan Patent Office. A copy and English translation was submitted before the USPTO on January 10, 2006.

Reconsideration and withdrawal of the anticipation rejection of claim 1 are respectfully requested.

Van Osch et al., *Plastics and Reconstructive Surgery*, 2001

Claims 1-4 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Van Osch et al., *Tissue Engineering*, 2000 (hereinafter referred to as "Van Osch II"). (*See*, Office Action, at pages 6-7). Applicant traverses the rejection as set forth herein.

Again, Applicant insists that the Examiner has either misinterpreted or misunderstood the disclosure of the reference cited. Thus, there are incorrect scientific conclusions drawn by the Examiner, explained in more detail as follows.

First, although the Examiner asserts that Van Osch II teach perichondrium to be a new "young" autologous cartilage suitable for nasal septum perforation in a child, Van Osch II in fact only disclose that this new "young" autologous cartilage appeared to be a suitable graft ... to close the nasal septum perforation of a child. (*See*, Van Osch II, at page 322, INTRODUCTION, lines 8 to 10). Thus, Van Osch II do not say that perichondrium is a new "young" autologous cartilage, but that cartilage itself appeared to be a suitable graft. Therefore, the Examiner's assertion is inconsistent with the clear disclosure and words of Van Osch II and does not relate to the claimed subject matter.

Second, although the Examiner asserts that the perichondrium is known to possess chondrocytes, this is also incorrect. Because perichondrium exists in a cartilage apart from chondrocytes (*see*, Exhibit A, at page 132, Fig. 7-1), perichondrium do not possess chondrocytes,

but do possess chondrogenic cells. (*See*, *Id.*, at page 132, right column, second paragraph, lines 5 to 9). On this point, Van Osch II disclose the following: "The cambium layer of the perichondrium . . . containing chondroprogenitor cells." (*Id.*, at page 328, lines 13 to 14). Furthermore, Van Osch II discloses that "perichondrium . . . could be used as a source of chondrogenic cells." (*Id.*, at page 325, lines 12 to 11 from the bottom).

Thus, chondrogenic cells, or chondroprogenitor cells, are clearly distinguishable from chondrocytes.

Third, although the Examiner points out that the perichondrium explants were cultured and grown to form a monolayer, the culture of perichondrium explants of Van Osch II does not relate to the presently claimed subject matter, which is a method of co-culturing chondrocytes together with perichondrium.

In light of the above scientifically-based explanations and clarifications of the disclosure of Van Osch II, although the Examiner's sentence, *i.e.*, "co-culturing from a cartilage having chondrocytes and perichondrium" is not clear, at least it can be concluded that Van Osch II do not explicitly disclose the method of the presently claimed invention, *i.e.*, a method of producing human chondrocytes by co-culturing human chondrocytes together with perichondrium, wherein said human chondrocytes are obtained from a human cartilage having said perichondrium.

Dependent claims 2-4 are not anticipated as, *inter alia*, depending from a non-anticipated base claim, claim 1.

Reconsideration and withdrawal of the anticipation rejection of claims 1-4 are respectfully requested.

Long et al., *Development*, 1998

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Long et al., *Development*, 1998 (hereinafter referred to as "Long et al."). (*See*, Office Action, at page 7). Applicant traverses the rejection as set forth herein.

Although the Examiner asserts that Long et al. disclose co-culturing chondrocytes together with the perichondrium, the Examiner's assertion is not supported by the disclosure of Long et al. for the following reasons.

Long et al. disclose a study in which they employed "an organ culture system." (*See*, Long et al., at page 1067, SUMMARY, left column, line 5, *emphasis added*). Tibiotarsi, which Long et al. used in their study, is an organ and Long et al. cultured tibiotarsi itself. (*See*, *Id.* at page 1068, left column, "Organ Culture"). The "organ culture system" of Long et al. may be a variable and unpredictable system. On the other hand, the method of the presently claimed invention does not culture cartilage itself but cultures chondrocytes, which are cells obtained from cartilage. The presently claimed method is referred to as a "cell culture system" in which exact conditions can be used, and thus is controllable. This is supported at least by the examples in the present specification.

Therefore, the "organ culture system" used by Long at al. is clearly distinguishable from the "cell culture system" utilized in the presently claimed method. Long et al. disclose an entirely unrelated method and do not disclose the method of the presently claimed invention.

Further, even in light of Long et al., just for the sake of discussion, Long et al. would not have provided the skilled person with a reasonable expectation of success in using the

perichondrium as presently claimed, since Long et al. disclose that "the perichondrium also negatively regulates the proliferation of chondrocytes." (*See*, *Id.*, page 1067, SUMMARY, left column, lines 3 to 2 from the bottom). Further it is disclosed that "the perichondrium negatively regulates both proliferation and differentiation of chondrocytes." (*See*, *Id.*, at page 1071, left column, lines 3 to 5). In light of this disclosure, one of ordinary skill in the art would not have any expected success in co-culturing chondrocytes together with perichondrium.

Thus, for the foregoing reasons, the disclosure of Long et al. cannot anticipate the presently claimed subject matter.

Reconsideration and withdrawal of the anticipation rejection of claim 1 are respectfully requested.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-4 stand rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over Hiroko et al. in view of Van Osch II or Klein-Nulend et al., as evidenced by Yi et al., Abstract, *J. Korean Soc. Plastic Reconst. Surg.*, 2001 (hereinafter, "Yi et al."). (*See*, Office Action, at pages 7-10). Applicant traverses the rejection as hereinafter set forth.

The Examiner's assertions regarding the disclosures of the references include many incorrect interpretations, as explained in more detail, below.

The Examiner states that "Hiroko et al. disclose a method of co-culturing human chondrocytes together with perichondrial cells." (*See*, *Id.*, at page 8, lines 6 to 7).

But, if interpreted properly, Hiroko et al. disclose only a method of co-culturing human

chondrocytes together with perichondrial cells in the chondrogenic stage as feeder cells. And the "perichondrial cells in the chondrogenic stage, as feeder cells" are obtained from a nonhuman mammalian fetus. (*See*, Hiroko et al., at paragraph [0008]).

On the other hand, the method of the presently claimed invention is:

"A method of producing human chondrocytes, wherein said method comprises: co-culturing human chondrocytes together with perichondrium, wherein said chondrocytes are obtained from a human cartilage having said perichondrium, and wherein no non-human animal feeder cells are present in the culture."

The method of the presently claimed invention uses "perichondrium" itself instead of "perichondrial cells in the chondrogenic stage." The "perichondrium" used in the method of the present invention is a membrane tissue surrounding a cartilage and obtained from the cartilage which provides chondrocytes to be cultured. The "perichondrium" of the presently claimed invention is not in the chondrogenic stage, as is the tissue utilized in Hiroko et al. According to the claim language of claim 1, the "perichondrium" and "chondrocytes to be cultured" are from the same origin, human.

Thus "perichondrial cells in the chondrogenic stage, as feeder cells" used in Hiroko et al. and "perichondrium" itself, used in the method of the present invention, are definitely distinguishable from each other.

Hiroko et al. is entirely silent with regard to the possibility of using a human perichondrium, let alone the employment of material derived from the same origin. A person of ordinary skill in the art, trying to improve the method described in Hiroko et al. would therefore

not derive from Hiroko et al., any incentive to switch from non-human feeder cells to the perichondrium itself.

Regarding Van Osch II, the Examiner's assertions again include many incorrect interpretations.

First, although the Examiner asserts that Van Osch II teach perichondrium to be a new "young" autologous cartilage suitable for a nasal septum perforation in a child, Van Osch II just describe that this new "young" autologous cartilage appeared to be a suitable graft ... to close the nasal septum perforation of a child, as also discussed in further detail, above, concerning the anticipation rejection over the same reference. (*See*, Van Osch II, at page 322, INTRODUCTION, lines 8-10).

Thus, Van Osch II do not disclose that perichondrium is a new "young" autologous cartilage, but rather Van Osch II disclose that the cartilage appeared to be a suitable graft. The Examiner's assertion is incorrect and does not relate to the claimed subject matter.

Second, although the Examiner asserts that the perichondrium is known to possess the chondrocytes, this is also incorrect, because perichondrium exists in a cartilage which is separate from chondrocytes. (*See*, Exhibit A, at page 132, Fig. 7-1). Perichondrium do not possess chondrocytes but instead possess only chondrogenic cells (*see*, *Id.*, at page 132, right column, second paragraph, lines 5-9) which are definitely distinguishable from the chondrocytes of the presently claimed invention. On this point, Van Osch II disclose the following: "The cambium layer of the perichondrium . . . containing chondroprogenitor cells." (*Id.*, at page 328, lines 13 to 14). Furthermore, Van Osch II discloses that "perichondrium . . . could be used as a source of

chondrogenic cells." (*Id.*, at page 325, lines 12 to 11 from the bottom).

Thus, chondrocytes are definitely distinguishable from the chondrogenic cells or chondroprogenitor cells of Van Osch II.

Third, although the Examiner asserts that the perichondrium is known to possess the ability to generate cartilage, this is incorrect. Perichondrium itself does not possess the ability to generate cartilage. Chondrogenic cells, or chondroprogenitor cells, contained in perichondrium, may differentiate into cartilage. This important concept, apparently missing from the Examiner's understanding, is critical to correctly understand the disclosure of Van Osch II.

In light of the above, it can be concluded that Van Osch II do not explicitly disclose or suggest the method of the present invention, *i.e.*, a method of producing human chondrocytes by co-culturing chondrocytes together with perichondrium, wherein said chondrocytes are obtained from a cartilage having said perichondrium.

The Examiner argues that Klein-Nulend et al. disclose that the perichondrium from ear or rib is a convenient source of cells with chondrogenic potential, *i.e.* chondrocytes. (*See*, Office Action, at page 8, the last line to page 9, line 1). This indicates that the Examiner equates "cells with chondrogenic potential" with "chondrocytes." But the Examiner's argument is scientifically unsupportable.

Histology of cartilage clearly shows that cartilage is composed of a peripheral thin layer of perichondrium and a thick and bulky part including chondrocytes, and that perichondrium exists in the cartilage apart from chondrocytes or independent of chondrocytes. (*See*, Exhibit A, at page 132, Fig. 7-1). According to the histology of cartilage, perichondrium does not contain

chondrocytes themselves, but contain "progenitor cells with chondrogenic potential," (*see*, Klein-Nulend et al., at page 305, Abstract, lines 4-5) which are referred to as "chondrogenic cells." (*See*, Exhibit A, at page 132, right column, second paragraph, lines 5-9).

The "progenitor cells with chondrogenic potential" are therefore distinguishable from "chondrocytes." Thus, contrary to the Examiner's belief, the perichondrium cannot be a source of chondrocytes.

Klein-Nulend et al. only disclose or suggest differentiation of progenitor cells contained in perichondrium to chondrocytes and do not disclose the method of culturing chondrocytes or co-culturing chondrocytes together with perichondrium. Klein-Nulend et al. therefore do not disclose or suggest the method of the present invention.

The Examiner's assertions concerning the interpretation of the disclosure of Yi at al. are also incorrect for the following reasons.

First, although the Examiner asserts that Yi et al. teach that the perichondrium is a new source of cartilage for auricular cartilage grafts, the disclosure of Yi et al. does not relate to *in vitro* cell culture, but rather relates to *in vivo* regeneration. Actually Yi et al. describes the following: "In various animal studies, perichondrium has been described as the source of new cartilage." (*See*, Yi et al., at lines 2 to 3). Yi et al. further state that: "In each experimental group, one of Alloderm . . . were implanted at the donor site of cartilage graft in New Zealand White rabbits ..." (*Id.*, at lines 8 to 10). Thus, "*in vivo* regeneration" is scientifically distinguishable from "*in vitro* cell culture" which is used in the method of the present invention, *i.e.*, co-culturing chondrocytes together with perichondrium.

Second, although the Examiner asserts that Yi et al. disclose grafts wherein the perichondrium is preserved, Yi et al. actually disclose that: "In group I (n=9), both (ventral & dorsal) sides perichondrium were preserved . . ." (*Id.*, at lines 11 to 12). This means that perichondrium was preserved in rabbits, not grafts. Thus, the Examiner's assertion is not correct and does not reasonably relate to the claimed subject matter.

Third, although the Examiner asserts that Yi et al. further suggest the perichondrium to produce chondrogenic cells, Yi et al. actually disclose that "[t]he template serves as an inducer for the perichondrium to produce chondrogenic cells." (*Id.*, at lines 6 to 4 from the bottom).

Thus, Yi et al. only disclose the role of a template in *in vivo* regeneration. Therefore, this disclosure of Yi et al. does not relate to the claimed subject matter.

Finally, although the Examiner asserts that Yi et al. further suggest that the perichondrium serves as a scaffold for cartilage differentiation, Yi et al. actually disclose that "[t]he template serves as a scaffold for the cartilage differentiation." (*Id.*, at lines 6 to 4 from the bottom). Correctly reading and understanding Yi et al., Yi et al. just disclose the role of template in regeneration *in vivo* of cartilage. Due to unpredictability within the art, it is commonly known in the field that a method that works well *in vivo* does not necessarily work identically well *in vitro*, and sometimes *vise versa*. Therefore it is clear that Yi et al. do not disclose or suggest the method of the presently claimed invention, *i.e.*, co-culturing chondrocytes together with perichondrium.

Although the Examiner asserts that given what is known in the art of the proliferative and differentiation abilities of the perichondrium, it's ability to generate and maintain characteristics

of cartilage, and it's chondrogenic potential, as taught by Van Osch II and Klein-Nulend et al., further supported by Yi et al., one of ordinary skill in the art would have been motivated to co-culture chondrocytes with it's perichondrium intact, these statements are not persuasive because, as described in detail, above, the scientific premises of the Examiner's assertion are factually incorrect and none of the cited references, *i.e.*, Hiroko et al., Van Osch II, Klein-Nulend et al. and Yi et al., considered in combination, disclose or suggest co-culturing chondrocytes with their perichondrium intact. The Examiner's assertion should therefore be considered nothing more than an attempt at improper hindsight reconstruction of Applicant's own invention.

Although the Examiner asserts that there is a need in the art for cells/tissues which are capable of supporting the proliferation and differentiation of chondrocytes, if so, need itself does not teach the means for solving the problem. This statement of the Examiner appears to further indicate an attempt at improper hindsight reconstruction.

Further, although the Examiner asserts that given the ability of the perichondrium to do so (supporting the proliferation and differentiation of chondrocytes) as is allegedly taught by Van Osch II and Klein-Nulend et al., further supported by Yi et al., one would have expected success in co-culturing chondrocytes with its intact perichondrium, this also is not persuasive because, none of the cited references disclose or suggest that the perichondrium would support the proliferation of chondrocytes. Therefore, this assertion of the Examiner should also be considered an improper attempt at hindsight reconstruction.

Thus, the presently claimed subject matter involves an inventive step over Hiroko et al., Van Osch II, Klein-Nulend et al. and Yi at al., in view of the fact that Hiroko at al., the technical

problem underlying the present invention may be seen as the provision of an alternative and improved method for the producing/culturing of chondrocytes.

Hiroko et al. disclose that chondrocytes should be cultured by using "non-human perichondrial cells in ... the chondrigenic stage as feeder cells." However, as has in the meantime become clear by the above discussion, the employment of such a strategy is rather disadvantageous, since animal feeder cells may cause unexpected bacterial or viral infections, whose prevention is complicated and time-consuming. (*See*, the present specification, at page 3, lines 1 to 4).

The presently claimed subject matter thus provides significant progress in the chondrocyte cultivation technique, since non-human animal feeder cells as described in Hiroko et al. are no longer necessary, according to the presently claimed method. None of the cited references disclose or suggest the means for solving the problem employed in the present invention.

Therefore, for at least the foregoing reasons, reconsideration and withdrawal of the obviousness rejection of claims 1-4 are respectfully requested.

CONCLUSION

If the Examiner has any questions or comments, please contact Thomas J. Siepmann, Ph.D., Registration No 57,374, at the offices of Birch, Stewart, Kolasch & Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: February 5, 2008

Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

Attachments:
Exhibit A - L.P. Gartner et al., *Color Textbook of Histology*, page 131-134, *inter alia*, page 132, Fig. 7-1.
Exhibit B - Graf et al., *International Orthopaedics*, 17:113-119, 1993.